PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing human papillomavirus vaccine concerns on Twitter: A cross-sectional study of users in Australia, Canada, and the United Kingdom
AUTHORS	Shapiro, Gilla; Surian, Didi; Dunn, Adam; Perry, Ryan; Kelaher, Margaret

VERSION 1 - REVIEW

REVIEWER	Prof. Heidi Larson, Dept. Infectious Disease Epidemiology London School of Hygiene & Tropical Medicine UK My research group has received funding ffrom GSK and Merck for educational symposia, and we receive funding from GSK to advise on vaccine hesitancy issues. We are part of two EU funded Innovative Medicines Initiative which have multiple industry partners.
REVIEW RETURNED	08-Apr-2017

GENERAL COMMENTS	Overall, this is an excellent paper. I recommend that in the "strengths and limitations" list of points, that the first point more specifically says "investigating how HPV vaccination concerns are expressed.." rather than stating ""vaccination concerns" more broadly which the paper did not examine On the third point " the study revealed the potential for misinformation and concerns to spread internationally", the paper did not really investigate this in any depth, although this could be rephrased in a way that says, " as the three countries chosen were all English-speaking countries there was a potential for misinformation to spread..."

REVIEWER	Maria Grandahl Department of Public Health and Caring Sciences; Department of Women's and Chlidren's Health, Uppsala University, Sweden
REVIEW RETURNED	30-Apr-2017

GENERAL COMMENTS	The authors conducted an international comparison investigating how vaccination concerns are expressed on Twitter. This is most relevant since vaccine concerns are a growing challenge and the coverages for HPV vaccine is lower compared to other childhood vaccinations in many countries.

	Introduction: It would be helpful with some more information about the national HPV vaccination programme (i.e. the context in the three countries) such as national HPV vaccine coverage, school-based, provided by school nurses, target group (gender, age, catch-up vaccination) etc. Results: The study is guided by HBM, thus it would be helpful with Tables presenting the results according to HBM in the main manuscript (such as Tables A3 and A4, supplemental files). Discussion: It would be great if the authors could include a discussion about the differences in concerns between the countries, why are their differences? And also add some more about differences in relation to the national vaccine coverages for HPV vaccine (and if possible also in relation to other childhood vaccinations in the national immunisation programmes, the authors already have some about this in the discussion lines 24-27).

REVIEWER	Barbara Rath, MD PhD Vienna Vaccine Safety Initiative Berlin, Germany
REVIEW RETURNED	12-May-2017

GENERAL COMMENTS	Major comments (1) Twitter is a global medium and it seems counterintuitive to limit the analysis to three English-speaking countries only while leaving out the most important twitter market in the US as well as English-speaking twitter accounts elsewhere in the world, in particular in developing countries. Ignoring these tweets based on geo-tagging introduces unnecessary bias and limits the usefulness of the data. As the authors state themselves, geo-tagging is of limited value with regard to the actual location of a smartphone user – whereas language settings do reflect how twitter networks actually function. it would be more informative to focus on specific HPV vaccine rumors and to study how they are spreading across the (English-speaking) world. (2) Analysis by type of sender (private individual, healthcare professional, stakeholder organization, parent, vaccine recipient, and so forth) would be critical to interpret the results. Regarding stakeholder organizations it may be important to learn whether official communication (by GAVI, CDC WHO and others) via twitter is effective and reaching the concerned users. Do twitter users share official information once they have voiced personal concerns? How fragmented is the twitter world? Can we detect and visualize communication “bubbles” In this context it will also be important to learn whether specific rumors spread individually or in clusters. (3) The categories chosen to classify types of concern are of limited

	value. These should be aligned with the published literature (incl. other types of social media, open-ended survey questions, focus groups etc.). The published literature is not sufficiently incorporated into the study design and in the interpretation of results. (see also Table 1) (4) As mentioned above, typical HPV-specific concerns and rumors and the pathway/evolution should be analyzed more in-depth. There are methods available to do that, and this might be the most interesting information to the reader. An overview of all concerns based on a limited time frame is of limited value given the impact of individual events on HPV vaccine acceptance. The tables 2 and 3 could be omitted or moved summarized briefly in the text as differences between UK, Canada and Australia were minimal and not of public health significance. Minor comments: Abstract - „International comparison investigating how vaccination concerns are expressed on Twitter“ be more specific. Which countries and which concerns. Please include all English-Language twitter accounts to get rid of a “blind spot” / major limitation of this study. Leaving out particular areas of the (English-speaking) world, especially US twitter accounts, would be ignoring one of the most significant user groups. - The abstract should avoid drawing conclusions that are not actually supported by the data. - The term “barrier” is used inconsistently throughout this manuscript. Most researchers would consider “barriers” as related to access to vaccines (cost, logistical or geographical barriers). This groups should not be confused methodologically with users, who would have perfect access to vaccines but decline to making use of them due to concerns about HPV vaccine safety or effectiveness, or concerns about cultural/religious sensitivities being affected by vaccine use. - “Twitter users who mostly expressed concerns about HPV vaccines were better connected to international users who shared their concerns” as opposed to whom/ which users? How was this measured? The basic numerical results should be expressed in the abstract. Methods

	- Is there a difference (in effect and impact) between tweets and re-tweets? How is this accounted for in the analysis? How do you account for repeated re-tweets by the same individual versus unique tweets? - The distinction between 'frequent tweeters' versus 'infrequent tweeters' is a bit unclear, as is the significance of tweets in relation to the user's radius/sphere of influence/number of followers. - Limiting tweets to a particular vaccine may help to focus the analysis, but it should be mentioned in the abstract/discussion/limitations that overall anti-vaccine attitudes are not reflected in this approach. - Regarding the classification of concerns: please refer to "Table 1" - Ethics approval: It is a bit unclear how and where the ethics approval was sought. Did the twitter users give consent? Who governs/owns this type of data? - Please address the limitations of categorizing concerns manually versus by machine learning algorithms (for consistency/reproducibility: what would be the search terms for future researchers should be using?) Results/ Conclusions: - Discuss the volatility of data: it seems like one user could change the outcome quickly depending on "incidents" and rumors. - What would be the key conclusions of public health stakeholders, how could the lessons leant be translated into effective future / interventions or communication strategies? - In what respect are HPV-vaccine related tweets different from general vaccine concerns? What is the impact of these differences? - You note that messages can be amplified to 16K to 500K users, what is the time frame and how much time would there be addressing misinformation or "fake news" (if any)? How? Who should be I charge of that? - In what aspect is twitter different from other types of social media? (this was mentioned only briefly in the discussion and needs more detail / placement in the context of the published literature. - "The predominance of 'barrier' concerns on Twitter indicates the importance of physicians discussing concerns" this conclusion cannot be drawn from the data presented P12 L 13 vs P11 L 48, P12 L30

	‘barrier’ concerns (i.e. safety, pain, side effects, logistical barriers)“ The term “barrier” should be defined narrowly and at the very beginning of the manuscript, and then used consistently throughout the manuscript. See also comments re: Table 1. Table 1: The classification should make use of universally accepted terminologies and categories in line with similar published studies available in the literature. Examples: - Use “effectiveness” instead of “unnecessary” (as the underlying concern are doubts about the benefits and effectiveness of the vaccine) - Safety concerns are key to the analysis of this study and should be labeled as such. - Avoid lumping actual vaccine-related (safety and effectiveness) concerns together with barriers due to cost or logistical matters (the latter should best be labeled “access”) - another groups should include any general concerns due to “lack of trust” (toward healthcare professionals, public health agencies, industry). These are of major relevance to stakeholders and should not be hidden under “other”. - A comment claiming that “the body does not need” a specific vaccine should be categorized as an effectiveness concern. In essence, as this statement questions whether the vaccine will provide any benefit to the recipient. - What is missing in a HPV-specific study is another category of religious/ethical/parental concerns. Parents may reject or postpone the vaccine as to avoid having to communicate sexual health topics ‘too soon’. This is mentioned only briefly in the manuscript, but this important aspect, which is unique to HPV vaccine, should be developed further. (and the appropriate age to do so) should be delineated more clearly. - Lastly, the “no concern” group should allow for additional subcategories. This study provides the data to analyze the pathways of explicitly positive comments/tweets as opposed to tweets that are indifferent or delegating the decision-making to others (healthcare providers, family members, religious leaders and so forth). Tables 2 and 3: Unless significant differences are observed, these results can be

	omitted summarized in the text. The tables should be replaced by additional graphic representations of twitter networks illustrating (a) the spread of specific HPV vaccine-related rumors over time and (b) the distribution and significance of critical users (even if anonymized) across the English-speaking twitter-sphere. Figure 1: The significance of the findings should be explained in greater detail in the text. What can be learned from the Figure? What can be said about clusters in the periphery versus the center of the image? and how could the interconnectedness of the messages related to the same topic be visualized more clearly? Consider serial imaging to show how tweets voicing specific types of concerns are spreading over time. Figure 2: This graph is more informative. Again, separating explicitly positive from explicitly negative comments may be more helpful here. This would be relevant to public health stakeholders who wish to whether pro-vaccine versus anti-vaccine statements travel differently.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Prof. Heidi Larson, Dept. Infectious Disease Epidemiology
Institution and Country: London School of Hygiene & Tropical Medicine, UK
Please state any competing interests: My research group has received funding ffrom GSK and Merck for educational symposia, and we receive funding from GSK to advise on vaccine hesitancy issues. We are part of two EU funded Innovative Medicines Initiative which have multiple industry partners.

Please leave your comments for the authors below

Overall, this is an excellent paper.

I recommend that in the "strengths and limitations" list of points, that the first point more specifically says "investigating how HPV vaccination concerns are expressed.." rather than stating ""vaccination concerns" more broadly which the paper did not examine

***Thank you for this comment. This has now been changed as recommended (page 4).

On the third point " the study revealed the potential for misinformation and concerns to spread internationally", the paper did not really investigate this in any depth, although this could be rephrased in a way that says, " as the three countries chosen were all English-speaking countries there was a potential for misinformation to spread..."

***Thank you for this comment. To highlight that the study was conducted in English-speaking countries, we now write “The analysis of social connections among Twitter users posting about HPV vaccines in three English-speaking countries (Australia, Canada, and the United Kingdom) revealed the potential for concerns to spread internationally” (page 4).

Reviewer: 2
Reviewer Name: Maria Grandahl
Institution and Country: Department of Public Health and Caring Sciences; Department of Women's and Chlidren's Health, Uppsala University, Sweden
Please state any competing interests: None declared

Please leave your comments for the authors below

Thank you for the opportunity to read this interesting and well-written paper guided by HBM. The authors conducted an international comparison investigating how vaccination concerns are expressed on Twitter. This is most relevant since vaccine concerns are a growing challenge and the coverages for HPV vaccine is lower compared to other childhood vaccinations in many countries.

Introduction: It would be helpful with some more information about the national HPV vaccination programme (i.e. the context in the three countries) such as national HPV vaccine coverage, school-based, provided by school nurses, target group (gender, age, catch-up vaccination) etc.

***Thank you for this comment. We had originally included this information but deleted it due to the journal’s word limits. We agree with the reviewer that this information is important to include and therefore now write, “There is notable variation between countries’ HPV vaccine programs and coverage rates.

Australia’s school-based vaccination program targets 12-13 year olds females (since 2007) and males (since 2013).13 According to Australia’s National HPV vaccination program register, 85.6% of females and 77% of males received the HPV vaccine (2015 data).14,15 In Canada, all provinces and territories introduced school-based vaccination programs for 9-13 year old females (2007-2010), and six provinces also include boys in HPV vaccine programs (since 2013).16 According to national parental surveys, 72.3% of females (2013 data) and less than 3% of males received the HPV vaccine (2014 data).17-19 Lastly, the United Kingdom (UK) only provides a school-based vaccination program for 12-13 year old females (since 2008). According to Public Health England, 89.5% of females in the UK received the HPV vaccine (2015 data).20 HPV vaccine coverage rates are lower than other child or adolescent vaccines in these countries national immunisation programs;21-23 suboptimal coverage hinders cancer prevention efforts.24” (please see the Introduction, page 5, paragraph 2).

Results: The study is guided by HBM, thus it would be helpful with Tables presenting the results according to HBM in the main manuscript (such as Tables A3 and A4, supplemental files).

***Thank you for your comment. Given a small numbers of the tweets for certain HBM categories (see Tables A1 and A2), the multi-class classifier could not accurately distinguish between these HBM categories when coding thousands of tweets based on the HBM coding scheme. Accordingly, specific

types of HBM concerns were combined (see Table 1, A2). Combining categories was done based on conceptual similarity and trying to remain as true to the HBM as possible while attaining accuracy of the classifier. By combining some categories in this way, we were able to produce more reliably and robust classifiers. In the manuscript, we now add that “Combining categories was done based on conceptual similarity and trying to remain as true to the HBM as possible while attaining accuracy of the classifier” (page 9).

Table A3 relates to the binary classifier. Table A4 relates to the multi-class classifier (using the combined groups discussed in A2 and Table 1).

Discussion: It would be great if the authors could include a discussion about the differences in concerns between the countries, why are their differences? And also add some more about differences in relation to the national vaccine coverages for HPV vaccine (and if possible also in relation to other childhood vaccinations in the national immunisation programmes, the authors already have some about this in the discussion lines 24-27).

***Thank you for this comment. In the first paragraph of the Discussion (page 12) we have added proportions to help the reader better identify the differences between the countries. We now write, “Canadian Twitter users less often expressed concerns about HPV vaccines (14.9%) compared to Australia (19.3%) and the UK (22.6%) (Table 2). There was a general consistency in the proportions of specific concerns across the three countries, and the most common concerns (46%) were related to ‘perceived barriers’ (i.e. logistical challenges and psychological barriers such as perceived harms of receiving the HPV vaccine) (Table 3).”

Although our study is not able to test the relationship between coverage rates and Twitter use, to provide the reader with context, in the Introduction, we have also included national vaccine coverage rates (as well as comparison to other childhood vaccination in national immunization programs) for HPV vaccination in the Introduction alongside information on the programs of these countries (as suggested above).

Reviewer: 3
Reviewer Name: Barbara Rath, MD PhD
Institution and Country: Vienna Vaccine Safety Initiative, Berlin, Germany
Please state any competing interests: None declared

Please leave your comments for the authors below

BMJ Open Review

Shapiro G et al. HPV vaccine concern on Twitter: A cross-country evaluation of Australia, Canada, and the United Kingdom

Summary
The authors conducted a descriptive /comparative analysis of English language HPV-related tweets in Australia, Canada and the UK, aiming to assess the level and types of concerns expressed in twitter as a major social media network. The authors are using machine learning algorithms and the twitter API to delineate areas of concern.

The paper addresses an important knowledge gap – the spread of vaccine-related sentiments scares

via twitter. Given the amount of data available to the authors and the effort undertaken to categorize vaccine concerns, the analysis comes short. Significant improvements can be made to the study design and analysis to increase the value of the manuscript to the readers.

***We thank the reviewer for her helpful comments and have addressed each, point-by-point. For clarity, we have added numbers to each comment below.

Major comments

(1) Twitter is a global medium and it seems counterintuitive to limit the analysis to three English-speaking countries only while leaving out the most important twitter market in the US as well as English-speaking twitter accounts elsewhere in the world, in particular in developing countries. Ignoring these tweets based on geo-tagging introduces unnecessary bias and limits the usefulness of the data. As the authors state themselves, geo-tagging is of limited value with regard to the actual location of a smartphone user – whereas language settings do reflect how twitter networks actually function. it would be more informative to focus on specific HPV vaccine rumors and to study how they are spreading across the (English-speaking) world.

***Thank you very much for this comment. This study aimed to compare three countries that are similar. This has now been made clearer in “Study Overview” (page 7) where we write: “These countries were selected because they are English-speaking countries, share a similar history and commonwealth membership, and their similarity in administering the HPV vaccination in schools.” Furthermore, there has been some research conducted on HPV vaccine concerns on twitter in the U.S. We now also directly cite this work and compare our findings with this research. In the Discussion (page 13) we now write, “… a study of six months of Twitter data in the United States (between October 2013 and April 2014) found 25.1% of tweets were negative.” Furthermore, as a limitation (Discussion, page 15), we now write: “the study was limited to English-language tweets in three countries and evaluations of other countries and other languages may have yielded different results. It would be beneficial for future research to expand the focus of analysis to examine diverse countries, as well as conduct more nuanced regional explorations of a single country.”

(2) Analysis by type of sender (private individual, healthcare professional, stakeholder organization, parent, vaccine recipient, and so forth) would be critical to interpret the results. Regarding stakeholder organizations it may be important to learn whether official communication (by GAVI, CDC WHO and others) via twitter is effective and reaching the concerned users. Do twitter users share official information once they have voiced personal concerns? How fragmented is the twitter world? Can we detect and visualize communication “bubbles” In this context it will also be important to learn whether specific rumors spread individually or in clusters.

***Thank you very much for this comment. Modelling and characterisation of Twitter users is an emerging research area that is useful in understanding how different types of users contribute in social media, but one that we did not implement here because it does not directly address the objective of the study. Instead of characterizing users by type (such as organisations, scientists, parents, anti-vaccine advocates), we characterized users by their country and whether or not they expressed concerns. To clarify, we have modified the manuscript to say, “…it is important for further research to analyse results by type of sender.” (please see the Discussion, page 14)

(3) The categories chosen to classify types of concern are of limited value. These should be aligned with the published literature (incl. other types of social media, open-ended survey questions, focus

groups etc.). The published literature is not sufficiently incorporated into the study design and in the interpretation of results. (see also Table 1)

***This study sought to use a theoretical model, the Health Belief Model, to guide our coding. The Health Belief Model is one of the most widely used theories in the field of Health Psychology, and has been often used in understanding HPV vaccine attitudes and vaccine behaviour (for a review please see Glanz et al. 2008, http://hbcs.ntu.edu.tw/uploads/bulletin_file/file/568a39ae9ff546da4e02eb72/Health_behavior_and_health_education.pdf, Table 3.1). To account for additional prominent concerns that were not captured by the model but are present in the literature, our coding scheme was also informed by a thorough search of the literature (including content analyses of media and social media related to the HPV vaccine as well as research on vaccine hesitancy). Other codes that were prevalent in the HPV vaccine literature and therefore included into our coding scheme were: mistrust, undermining of religious principles, undermining of civil liberties, additional concerns (not otherwise specified), and ambiguous tweets. References from the literature that were used to guide our coding scheme are listed below (1-20).

In an iterative process, we then narrowed our coding scheme from over 25 categories to a more workable 12 categories, which were used in the manual coding of tweets. Given the very small number of tweets obtained for certain codes (see Tables A1 and A2), the multi-class classifier could not accurately distinguish between some categories when coding thousands of tweets based on the 12-group coding scheme. Categories were therefore collapsed based on conceptual similarity and trying to remain as true to the theoretical model as possible, while ensuring accuracy of the classifier was achieved.

Literature that informed our coding scheme include:

[1] Donadiki EM, Jiménez-García R, Hernández-Barrera V, Sourtzi P, Carrasco-Garrido P, López de Andrés A, et al. Health Belief Model applied to non-compliance with HPV vaccine among female university students. Public Health. 2014;128:268-73.
[2] Krawczyk A, Knäuper B, Gilca V, Dubé E, Perez S, Joyal-Desmarais K, et al. Parents' decision-making about the human papillomavirus vaccine for their daughters: I. Quantitative results. Hum Vaccin Immunother. 2015;11:322-9.

[3] Briones R, Nan X, Madden K, Waks L. When vaccines go viral: an analysis of HPV vaccine coverage on YouTube. Health communication. 2012;27:478–85.
[4] Rosenstock IM. Historical origins of the health belief model Health Educ Monogr 1974;2:328-35.
[5] Perez S, Fedouruk C, Shapiro GK, Rosberger Z. Giving Boys a Shot: The HPV Vaccine's Portrayal in Canadian Newspapers. Health communication. 2016;31:1527-38.
[6] Perez S, Shapiro GK, Brown CA, Dube E, Ogilvie G, Rosberger Z. 'I didn't even know boys could get the vaccine': Parents' reasons for human papillomavirus (HPV) vaccination decision making for their sons. Psycho-Oncology. 2015;[Epub ahead of print].
[7] Larson H, Leask J, Aggett S, Sevdalis N, Thomson A. A Multidisciplinary Research Agenda for Understanding Vaccine-Related Decisions. Vaccines. 2013;1:293-304.
[8] Larson HJ, Jarrett C, Schulz WS, Chaudhuri M, Zhou Y, Dube E, et al. Measuring vaccine hesitancy: The development of a survey tool. Vaccine. 2015.
[9] Britt RK, Hatten KN, Chappuis SO. Perceived behavioral control, intention to get vaccinated, and usage of online information about the human papillomavirus vaccine. Health psychology and behavioral medicine. 2014;2:52-65.
[10] Casciotti DM, Smith KC, Tsui A, Klassen AC. Discussions of adolescent sexuality in news media coverage of the HPV vaccine. Journal of adolescence. 2014;37:133-43.
[11] Casciotti DM, Smith KC, Andon L, Vernick J, Tsui A, Klassen AC. Print news coverage of school-based human papillomavirus vaccine mandates. The Journal of school health. 2014;84:71-81.

[12] Madden K, Nan X, Briones R, Waks L. Sorting through search results: a content analysis of HPV vaccine information online. Vaccine. 2012;30:3741-6.
[13] Nan X, Daily K. Biased assimilation and need for closure: Examining the effects of mixed blogs on vaccine-related beliefs. Journal of health communication. 2015;20:462-71.
[14] Feinberg Y, Pereira JA, Quach S, Kwong JC, Crowcroft NS, Wilson SE, et al. Understanding Public Perceptions of the HPV Vaccination Based on Online Comments to Canadian News Articles. PloS one. 2015;10:e0129587.
[15] Thomson A, Robinson K, Vallee-Tourangeau G. The 5As: A practical taxonomy for the determinants of vaccine uptake. Vaccine. 2016;34:1018-24.
[16] Keelan J, Pavri V, Balakrishnan R, Wilson K. An analysis of the Human Papilloma Virus vaccine debate on MySpace blogs. Vaccine. 2010;28:1535-40.
[17] Wolfe RM, Sharp LK, Lipsky MS. Content and design attributes of antivaccination web sites. JAMA. 2002;287:3245-8.
[18] Keelan J, Pavri-Garcia V, Tomlinson G, Wilson K. YouTube as a source of information on immunization: A content analysis. JAMA. 2007;298:2482-4.
[19] Abdelmutti N, Hoffman-Goetz L. Risk messages about HPV, cervical cancer, and the HPV vaccine Gardasil: A content analysis of Canadian and U.S. national newspaper articles. Women & health. 2009;49:422-40.
[20] Habel MA, Liddon N, Stryker JE. The HPV vaccine: A content analysis of online news stories. J Womens Health. 2009;18:401-7.

(4) As mentioned above, typical HPV-specific concerns and rumors and the pathway/evolution should be analyzed more in-depth. There are methods available to do that, and this might be the most interesting information to the reader.

***Thank you for this comment. Monitoring the pathways of concerns in these three English-speaking countries would be a very interesting follow-up study; however, we believe that doing so is outside the scope of this manuscript. The state-of-the-art methods for tracking the provenance and spread of misinformation on Twitter are based on hashtags and not on stories that may have multiple external websites as injections, so the methods are not yet capable of achieving the level of rigour we would need to implement them here. We have therefore emphasized this as an important future direction in the manuscript. We write,

"Further research would be beneficial to assess the pathway of HPV vaccine concerns, and whether such concerns have a real-world impact (e.g. on vaccine coverage)" (please see page 14).

An overview of all concerns based on a limited time frame is of limited value given the impact of individual events on HPV vaccine acceptance.

***Relative to other research in the area, ours is among the longest and largest collection of HPV vaccine tweets (Dunn et al. 2015; Surian et al. 2016). To make a comparison, we now write (page 15), "Two studies have independently examined responses on Twitter to specific controversial events including US Representative Michele Bachmann's claim that HPV vaccines could cause "mental retardation", and Katie Couric's television segment "HPV Vaccine Controversy" that aired on December 4, 2013 53,75. Mahoney et al. (2015) evaluated 200 social media posts before and after Bachmann's comments on the Today Show and found that though most media was positive in tone, compared to Google News, Twitter disseminated more positive HPV vaccine articles and also used more personal accounts as a reference source 53. In contrast, using a random sample of 3,595 tweets, Bahk et al. (2016) found that most sentiment on Twitter towards HPV vaccines before Katie Couric's episode was negative, and while there was a decrease of negative sentiment immediately after the show aired, negative sentiment returned to baseline after two weeks 75. Future research should also investigate how public health organizations should effectively intervene to curb

misinformation or ‘fake news’ regarding HPV vaccination.”

The tables 2 and 3 could be omitted or moved summarized briefly in the text as differences between UK, Canada and Australia were minimal and not of public health significance.

***Please see comment 23, where this is addressed.

Minor comments:

Abstract
(5) „International comparison investigating how vaccination concerns are expressed on Twitter“ be more specific. Which countries and which concerns.

***This has been modified as recommended (please see page 2). Thank you.

(6) Please include all English-Language twitter accounts to get rid of a “blind spot” / major limitation of this study. Leaving out particular areas of the (English-speaking) world, especially US twitter accounts, would be ignoring one of the most significant user groups.

***Thank you for your comment. We have specified in the Abstract which countries we compared in this Analysis. This comment has been addressed above (see comment 1). Further, in our discussion of limitations we now write, “… the study was limited to English-language tweets in three countries and evaluations of other countries and other languages may have yielded different results” (page 15).

(7) The abstract should avoid drawing conclusions that are not actually supported by the data.

***Thank you for this helpful comment. The abstract has been modified as recommended (please see pages 2-3).

(8) The term “barrier” is used inconsistently throughout this manuscript. Most researchers would consider “barriers” as related to access to vaccines (cost, logistical or geographical barriers). This groups should not be confused methodologically with users, who would have perfect access to vaccines but decline to making use of them due to concerns about HPV vaccine safety or effectiveness, or concerns about cultural/religious sensitivities being affected by vaccine use.

***Thank you for this helpful comment. In this study, we used a theoretical model widely used in the Health Psychology literature—the Health Belief Model—to inform our coding scheme. As Glanz et al. (2008; http://hbcs.ntu.edu.tw/uploads/bulletin_file/file/568a39ae9ff546da4e02eb72/Health_behavior_and_health_education.pdf, Table 3.1) describes, ‘perceived barriers’ is the “belief about the tangible and psychological costs of the advised action”. Applying this definition (as specified by the theoretical model) conflates the tangible (e.g. logistical barriers such as affordability and accessibility) with the psychological costs (e.g. physical harms such as vaccine injection pain, safety, or side effects) (Table 1). We originally had sought to keep these codes separate (despite the Health Beliefs Model conflation); however, given the extremely few number of tweets about Logistical barriers in the manual coding of 1000 tweets (0.018%, see table A1 in Supplementary Information), these two groups regarding ‘perceived barriers’ were therefore merged in order to attain accuracy when using the multi-class classifier and in accordance with the Health Belief Model theory.

We have now made this clearer in the manuscript and now define barriers in accordance with the Health Belief Model (please see page 8-9): "…perceived barriers of HPV vaccination (including tangible barriers such as logistical challenges and psychological barriers such as perceived harms of receiving the HPV vaccine)…" We have also modified this throughout the manuscript (pages 2, 9, 12, and 13), in Table 1, and in Table A1.

(9) "Twitter users who mostly expressed concerns about HPV vaccines were better connected to international users who shared their concerns" as opposed to whom/ which users? How was this measured? The basic numerical results should be expressed in the abstract.

***This information can be found in Figure 2. We now make this clearer in the Abstract (page 3). We write, "Twitter users who mostly expressed concerns about HPV vaccines were better connected to international users who shared their concerns compared to Twitter uses who did not express concerns about HPV vaccines". Although we would have liked to include numerical results for this sentence in the abstract, there is too much detail to include (as we would have to express this comparison for each country, following each country; 12 results).

Methods

(10) Is there a difference (in effect and impact) between tweets and re-tweets? How is this accounted for in the analysis? How do you account for repeated re-tweets by the same individual versus unique tweets? The distinction between 'frequent tweeters' versus 'infrequent tweeters' is a bit unclear, as is the significance of tweets in relation to the user's radius/sphere of influence/number of followers.

***The only way to evaluate the impact of a specific tweet is to count the number of retweets, replies, or followers (the number of views is not available to anyone other than the user). The strongest indicator of impact is generally the number of followers but actual impact can vary independently (such is the nature of a network of interactions). We account for differences in potential impact through the surrogate of the number of followers in the analysis by counting the total number of potential exposures (aggregating the number of followers). In the manuscript we write, "While some argue that interaction with content (liking or retweeting) is a better measure of impact than followers, others have argued that many users on Twitter are passive and do not interact with the content, and as such followers may be a better indicator of impact. As this study examined follower networks, it would be helpful for future research to compare followers to different ways of interacting with content in order to better understand the impact of HPV vaccine tweets" (page 16).

(11) Limiting tweets to a particular vaccine may help to focus the analysis, but it should be mentioned in the abstract/discussion/limitations that overall anti-vaccine attitudes are not reflected in this approach.

***We agree with the reviewer and have included this as a future direction in the Discussion (page 13). We write, "It would be valuable to extend this work to examine differences in general vaccine concerns as well as compare concerns towards specific vaccines on Twitter."

(12) Regarding the classification of concerns: please refer to "Table 1"

***This comment has been addressed elsewhere (please see comments 3 and 8).

(13) Ethics approval: It is a bit unclear how and where the ethics approval was sought. Did the twitter users give consent? Who governs/owns this type of data?

***Thank you for this comment. In the manuscript we write, “The Macquarie University Human Research Ethics Committee (#5201401028) and the University of Melbourne’s Research Ethics Board (#1647488.1) provided ethics approval for data collection and analysis.” Researchers at Macquarie University govern and own this data.

As this data is available in the public domain, REB approval did not require Twitter users to give consent. To protect individuals’ privacy, any personal data was deliberately excluded or de-identified (e.g. domain names were deliberately excluded in Table 1). We have not updated the manuscript in relation to this comment.

(14) Please address the limitations of categorizing concerns manually versus by machine learning algorithms (for consistency/reproducibility: what would be the search terms for future researchers should be using?)

***The major strength of machine learning algorithms is that it allows for the coding of thousands of tweets. In contrast, manual coding can only examine fewer tweets of a more specific time frame (and is therefore less representative or generalizable, introducing external validity concerns). However, a limitation of machine learning algorithms is that this method may be less accurate and consistent compared to manual coding of tweets. To control for this limitation, our study examined the proportions of different types of concerns in the sample and the accuracy of the multi-class classifier. This is described in the manuscript and in greater length in the Supplemental Material (Sections 3 and 4). In order to improve accuracy, types of concerns were therefore combined.

Furthermore, in the manuscript, we report our search terms: “The search terms were “Gardasil”, “Cervarix”, “hpv AND vaccin*”, and “cervical AND vaccin*”.” These can be used by future researchers to enhance consistency. We have not updated the manuscript in relation to this comment.

Results/ Conclusions:
(15) Discuss the volatility of data: it seems like one user could change the outcome quickly depending on “incidents” and rumors.

***The dataset covers all tweets that meet the search criteria for the period of time covered by the study. Because of the scale of the data we have collected over a substantial period of time, it is highly unlikely that the inclusion or exclusion of any specific user could have changed the results. For example, that dataset covers the period of time for several major mainstream media controversies and changes in policy in several countries, as well as the potential flow on effects of tweets from US-based Twitter users with millions of followers. We have not modified the manuscript in relation to this comment.

(16) What would be the key conclusions of public health stakeholders, how could the lessons leant be translated into effective future / interventions or communication strategies?

***Thank you for this comment. Our recommendation to public health stakeholders is that monitoring social media for international risks to attitudes and beliefs could be a useful way to mitigate the effects of events such as vaccine scares more quickly. In the manuscript we write: “Together with other

studies on the representation of HPV vaccines in the media, our results suggest that it would be useful to monitor early indications of negative influence on attitudes and beliefs on social media" (page 15). We also now write, "This research could be used to design public health interventions that address concerns about the HPV vaccine on Twitter. In particular, this study suggests that methods for addressing vaccine concerns may benefit from targeting concerns about perceived barriers to vaccination (including logistical challenges and psychological barriers such as vaccine pain, safety, and side effects as a consequence of receiving the HPV vaccine). In addition, further coordination of public health agencies internationally may mitigate vaccine scares" (page 16).

(17) In what respect are HPV-vaccine related tweets different from general vaccine concerns? What is the impact of these differences?

***Thank you for this comment. We did not investigate general vaccine concerns, so we are unable to comment on these differences directly. The comparison is important however, and we have modified the manuscript to include the following: "It would be valuable to extend this work to examine differences in general vaccine concerns…" (page 13).

(18) You note that messages can be amplified to 16K to 500K users, what is the time frame and how much time would there be addressing misinformation or "fake news" (if any)? How? Who should be I charge of that?

***Thank you for this comment. We believe that public health stakeholders have a role in addressing misinformation, and that doing so in a timely manner is important. In the manuscript we write: "Public health professionals and policymakers must therefore be able to monitor, rapidly identify, and react to such concerns (e.g. by providing evidence-based responses in real-time and strengthening their own international networks)" (see page 13). We also now write (on page 14): "Public health organizations seeking to improve the uptake of HPV vaccines may benefit from tools that help them monitor the impact of vaccine scares on social media in other countries in order to pre-empt and respond to misinformation locally."

(19) In what aspect is twitter different from other types of social media? (this was mentioned only briefly in the discussion and needs more detail / placement in the context of the published literature.

***Thank you for this comment. As recommended by the reviewer, we now provide additional information on Twitter and compare it to other forms of social media. In the Introduction we now explain that, "Twitter is a microblogging service, established in 2006, that has over 313 million users active monthly" (page 6). We also now expand in the Discussion that, "Though greater research is required, the balance of positive and negative content appears to vary by source whereby the majority of news content,37 online comments (in response to news articles),42 and tweets have been found to be positive; the majority of YouTube content has been found to be negative.47" (page 13). In the limitations we now also clarify that Twitter (like all other social media and most surveys) are a potentially biased sample of the population: "Twitter is an inherently biased representation of the broader population, and is skewed both in terms of age and socioeconomics.80-83" (page 15).

(20) "The predominance of 'barrier' concerns on Twitter indicates the importance of physicians discussing concerns" this conclusion cannot be drawn from the data presented

***Thank you for this comment. We agree with the reviewer and modified the manuscript accordingly

(pages 13 and 16).

(21) P12 L 13 vs P11 L 48, P12 L30
'barrier' concerns (i.e. safety, pain, side effects, logistical barriers)"
The term "barrier" should be defined narrowly and at the very beginning of the manuscript, and then used consistently throughout the manuscript. See also comments re: Table 1.

***This is addressed above (please see comment 8).

(22) Table 1:
The classification should make use of universally accepted terminologies and categories in line with similar published studies available in the literature.
Examples:
- Use "effectiveness" instead of "unnecessary" (as the underlying concern are doubts about the benefits and effectiveness of the vaccine)
- Safety concerns are key to the analysis of this study and should be labeled as such.
- Avoid lumping actual vaccine-related (safety and effectiveness) concerns together with barriers due to cost or logistical matters (the latter should best be labeled "access")
- another groups should include any general concerns due to "lack of trust" (toward healthcare professionals, public health agencies, industry). These are of major relevance to stakeholders and should not be hidden under "other".
- A comment claiming that "the body does not need" a specific vaccine should be categorized as an effectiveness concern. In essence, as this statement questions whether the vaccine will provide any benefit to the recipient.
- What is missing in a HPV-specific study is another category of religious/ethical/parental concerns. Parents may reject or postpone the vaccine as to avoid having to communicate sexual health topics 'too soon'. This is mentioned only briefly in the manuscript, but this important aspect, which is unique to HPV vaccine, should be developed further. (and the appropriate age to do so) should be delineated more clearly.
- Lastly, the "no concern" group should allow for additional subcategories. This study provides the data to analyze the pathways of explicitly positive comments/tweets as opposed to tweets that are indifferent or delegating the decision-making to others (healthcare providers, family members, religious leaders and so forth).

***Please see responses to Comment 3 and 8, where these have been addressed. In addition, similar to our comments above, we had originally sought to keep separate concerns regarding mistrust, religious principles, civil liberties …etc. (please see Table A1 in Supplementary Information). However, given the extremely few number of tweets about these concerns in the manual coding of 1000 tweets (Table A1), which impacted the accuracy of the multi-class classifier, these codes had to be combined.

(23) Tables 2 and 3:
Unless significant differences are observed, these results can be omitted summarized in the text. The tables should be replaced by additional graphic representations of twitter networks illustrating (a) the spread of specific HPV vaccine-related rumors over time and (b) the distribution and significance of critical users (even if anonymized) across the English-speaking twitter-sphere.

***Our preference is to present raw numbers as often as possible. We have not modified the manuscript in relation to the comment.

(24) Figure 1:
The significance of the findings should be explained in greater detail in the text. What can be learned from the Figure? What can be said about clusters in the periphery versus the center of the image? and how could the interconnectedness of the messages related to the same topic be visualized more clearly? Consider serial imaging to show how tweets voicing specific types of concerns are spreading over time.

***We thank the reviewer for this comment. As described in the Figure's note, the nodes in the periphery versus the centre demonstrate the lack of a connection between these users. We have modified the manuscript to include: "Users from the three countries were disproportionately more likely to be followed by users from the same country, creating clusters of users by country (Figure 1). Furthermore, users who expressed concerns about the HPV vaccines appear to be more tightly connected within the United Kingdom, compared to either Australia or Canada. Figure 1 also highlights that users discussing HPV vaccines in the United Kingdom are more often connected to users in Australia and Canada than users in Australia and Canada are connected to each other" (page 11).

The concerns do follow a burst-like pattern, where specific concerns that reach the level of mainstream media are more frequent, though we felt that a full examination of the temporal dynamics of concerns would make an already complicated analysis unwieldy and hard to read.

(25) Figure 2:
This graph is more informative. Again, separating explicitly positive from explicitly negative comments may be more helpful here. This would be relevant to public health stakeholders who wish to whether pro-vaccine versus anti-vaccine statements travel differently.

***Thank you for this comment. In Figure 2, the positive comments ("non-concern") are separated from negative comments ("concern") for each of the three countries, to produce six groups (as circles). The arrows represent the proportions of followers that come from each of the other five groups, which may help to indicate how concerns travel internationally compared to other tweets.

We now write, "To examine the proportion of followers of HPV vaccine tweets, Figure 2 examines "concern" and "non-concern" tweets for each of the three countries (to produce six groups represented as circles). Relative to users who did not express concern about HPV, users that did express concerns had a higher proportion of international followers who also expressed concerns (Figure 2)" (pages 11-12).

VERSION 2 – REVIEW

REVIEWER	Professor Heidi Larson London School of Hygiene & Tropical Medicine UK The research group I lead has received funding from GSK and Merck to convene research symposium, we have done consulting for GSK on vaccine hesitancy issues, and HL served on the Strategic Advisory Board for Merck Vaccines from 2012-2014.
REVIEW RETURNED	19-Jun-2017

GENERAL COMMENTS	As this is the second round of reviews, I only have one comment which I think needs a small revision and one spelling correction. 1) In the third paragraph of the Discussion session, there is a revised sentence which has no basis. Its says that in order for public health organizations to improve HPV uptake, they should monitor the impact of vaccine scares on social media in other countries(?) in order to respond to misinformation locally(??) Most research on vaccine hesitancy states that responding to local issues needs an understanding of local concerns (not just awareness of other countries). I understand the value of monitoring what is going on in other countries vis a vis vaccine concerns, but that is not enough to inform local responses. 2) In the third paragraph of the Introduction "Columbia" is a misspelling. It should read Colombia.

REVIEWER	Maria Grandahl, Senior Lecturer Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
REVIEW RETURNED	14-Jun-2017

GENERAL COMMENTS	The authors have made substantial revisions. I recommend the manuscript for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Professor Heidi Larson
Institution and Country: London School of Hygiene & Tropical Medicine, UK

Please state any competing interests: The research group I lead has received funding from GSK and Merck to convene research symposium, we have done consulting for GSK on vaccine hesitancy issues, and HL served on the Strategic Advisory Board for Merck Vaccines from 2012-2014.

Please leave your comments for the authors below

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***Thank you very much for this comment. We have now modified this sentence to emphasize that it is important to understand both local and international concerns, and highlight the importance of further research in this area. We write, “Given the international connection between Twitter users who express concerns, public health organizations seeking to improve the uptake of HPV vaccines may

benefit from tools that help them monitor the impact of vaccine scares on social media locally as well as in other countries in order to pre-empt and respond to misinformation. Greater research would be helpful to further investigate how public health organizations can monitor and intervene to address vaccine concerns."

2) In the third paragraph of the Introduction "Columbia" is a misspelling. It should read Colombia.

***Thank you very much for this comment. This has now been changed as recommended.

Reviewer: 2
Reviewer Name: Maria Grandahl, Senior Lecturer
Institution and Country: Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
Please state any competing interests: None declared
Please leave your comments for the authors below

The authors have made substantial revisions. I recommend the manuscript for publication.